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SYNTHESIS OF A NOVEL RING CONTRACTED ARTEMISININ DERIVATIVE.

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Abstract:- Bromoacetal **1** undergoes a novel ring contraction reaction to give the product **2** in the presence of DBU.

In connection with our program to synthesise new ring systems derived from artemisinin,[1-4] we herein report a facile synthesis of a hitherto unknown ring skeleton.

The bromoacetal **1** was prepared from dihydroartemisinin as reported earlier.[2] Treatment of the bromoacetal **1** with DBU in methylene chloride at room temperature gave a solid **2**, mp 100°C, in 85% yield after usual workup and purification.[5] Its I R indicated the presence of a formyl and the peroxide group. In addition, the signal at δ 5.8 (H_{11}) supports the presence of artemisinin ring system.[6] Use of triethylamine in place of DBU in the above reaction also gave the same product **2**.

As the aldehyde **2** was found to be relatively unstable, it was reduced to give the alcohol **3** as a solid.[7] Irradiation of OCH_2 signal displayed NOE on the signal assigned to H_{11}, thus confirming that the relative configuration of OCH_2 group is β since the configuration of H_{11} is β as in artemisinin.[8] The formation of the aldehyde **2** with a high stereoselectivity is interesting and it may involve an initial ring opening of D-ring of the bromoacetal **1**.

Treatment of dihydroartemisinin with the alcohol **3** in the presence of $BF_3.Et_2O$ gave the two diastereoisomers **4** and **5** in 2:1 ratio. The structures **4** (solid, mp 154-156°C, yield 40%) and **5** (solid, mp 100°C, yield 20%) were assigned on the basis of NMR spectral properties.[9] The derivatives **2-5** were tested for blood schizonticidal activity in the mice model with P.berghei k-173 infection and the doses given subcutaneously on each of 5 consecutive days. The derivatives **2** and **3** had an ED_{90} of 25 mg/Kg and the ED_{90} of **4** and **5** were 1.25 and 2.5, respectively. The ED_{90} of arteether[6] and of the derivative[10] **6** were 1.25 and

10, respectively. The detailed biological profile of these derivatives will be published elsewhere.

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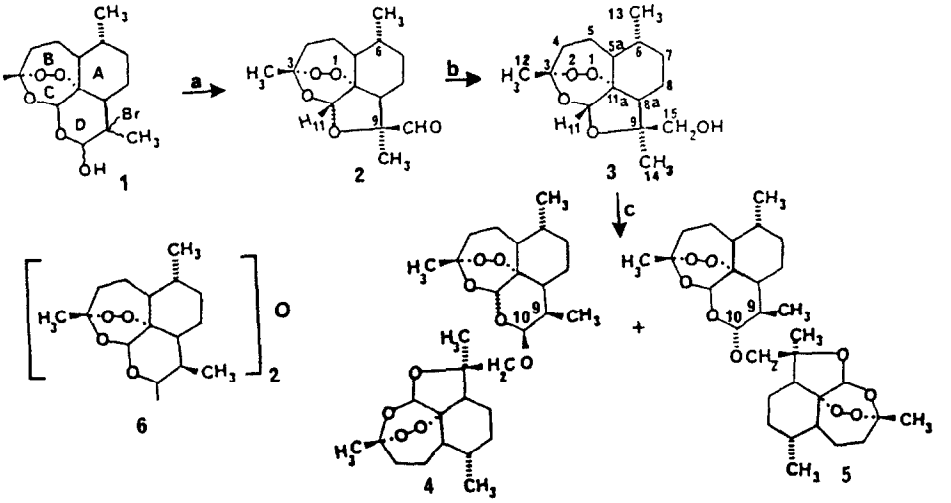

a. DBU; b. $NaBH_4$; c. BF_3Et_2O/ Dihydroartemisinin.

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5. Compound **2**. Solid mp 100°C, yield 85%. Mass Spect. m/e M+ 282, M - CHO 253. IR (KBr, cm^{-1}): 1740(CO),830,885,1130(peroxide). Analysis Caclcd. for $C_{15}H_{22}O_5$.Calcd.(Found): C,63.81(63.72),H,7.85 (7.92). ^{1}H-NMR ($CDCl_3$): δ 9.7(s,1H,CHO),5.8(s,1H,H_{11}),1.66(s,3-Me), 1.52(s,9-Me),1.0(d,6-Me).
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7. Compound **3**. Solid mp 135-136°C, yield 72%. Analysis Calcd. for $C_{15}H_{24}O_5$. Calcd.(Found): C,63.36(63.40),H,8.51(8.60). ^{1}H-NMR ($CDCl_3$): δ 5.6(s,1H,H_{11}),3.55(two d,J=11.5Hz,OCH_2),1.6(s,3-Me), 1.5(s,9-Me),1.0(d,6-Me). ^{13}C-NMR ($CDCl_3$): δ 19.38(13-Me),24.2(14-Me), 24.5(12-Me),25.13(C_8),25.3(C_5),32.7(C_7),36.95(C_4),37.38(C_6),49.3 (C_{8a}),51.7(C_{5a}),67.5(C_{15}),84.73(C_{11a}),87.07(C_9),97.09(C_{11}),103.59 (C_3). NOE: OCH_2 --► H_{11}. IR (KBr, cm^{-1}): 3420(OH),830,885,1120.
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9. The large $^3J_{H10/H9}$ (9.2Hz) observed in **5** is indicative of a trans diaxial coupling between H_{10} and H_9, hence H_{10} was assigned to a β configuration. The $^3J_{H10/H9}$ value of 3.6 Hz in **4** suggests a α configuration for H_{10}. Compounds **4** and **5** gave satisfactory elemental analysis.
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